Int J Clin Exp Med 2020;13(5):3489-3493
www.ijcem.com /ISSN:1940-5901/IJCEM0107222

Original Article

Progressive multifocal leukoencephalopathy (PML) after first-line, single agent ibrutinib therapy in a patient with chronic lymphocytic leukemia (CLL): a case report and literature review

Chakra P Chaulagain[1], Shakeel Tabish[2], Maria-Julia Diacovo[3], Fabian Candocia[4], Leah C Elson[1], Badih Adada[2], Camilo Garcia[2]

[1]Department of Hematology and Oncology, Maroone Cancer Center, Myeloma and Amyloidosis Program, Cleveland Clinic Florida, Weston, Florida, USA; Departments of [2]Neurology and Neurosurgery, [3]Pathology, [4]Radiology, Cleveland Clinic Florida, Weston, Florida, USA

Received December 31, 2019; Accepted February 21, 2020; Epub May 15, 2020; Published May 30, 2020

Abstract: Progressive Multifocal Leukoencephalopathy (PML) is a rare but often fatal opportunistic infection caused by the John Cunningham ("JC") virus in immunocompromised individuals. PML is usually described after multiple lines of immunochemotherapy often containing rituximab in patients with B-cell malignancies including chronic lymphocytic leukemia (CLL). The occurrence of PML after single agent ibrutinib for the treatment of CLL is extremely rare. We report a case of PML presented shortly after ibrutinib was initiated as the first-line monotherapy for the treatment of a patient with CLL. The patient presented with rapidly progressive neurologic symptoms that started two weeks after ibrutinib was started. An MRI of the brain was concerning for PML, but multiple CSF samples tested negative using a polymerase chain reaction for the JC virus. Finally, a brain biopsy clinched the diagnosis of PML. Unfortunately, the patient deteriorated over the next several weeks despite the discontinuation of ibrutinib and died from the PML. As ibrutinib has been moved up to the frontline setting for the treatment of CLL, it is important to increase awareness of the association of ibrutinib therapy to the occurrence of PML. The prognosis of PML remains poor despite a prompt diagnosis and the withdrawal of ibrutinib to allow immune reconstitution.

Keywords: Ibrutinib, progressive multifocal leukoencephalopathy, chronic lymphocytic leukemia, immunosuppression

Introduction

Progressive multifocal leukoencephalopathy (PML) is a central nervous system demyelinating disease caused by the John Cunningham virus (or "JC" virus). The reactivation of the virus occurs almost exclusively in immunosuppressed patients, including those with acquired immune deficiency syndrome (AIDS), hematologic malignancies, autoimmune diseases and solid organ or hematopoietic stem cell transplant (HSCT) recipients [1, 2]. The diagnosis of PML has also been reported in patients receiving monoclonal antibodies (e.g. natalizumab, rituximab, alemtuzumab, brentuximab vedotin, ofatumumab, obinutuzumab etc.) and therapy with other immune suppressants (prednisone, methotrexate, cyclosporine, etc.) [3-5]. Reports of Bruton's tyrosine kinase (BTK) inhibitors, such as ibrutinib, contributing to the development of PML are extremely rare. Currently, BTK inhibitors are either approved for, or being investigated in, the treatment of many hematologic malignancies [6]. Therefore, it is important to be aware of the adverse side effects of ibrutinib, including those that are rare. Here, we present a case of a patient who developed PML immediately after being started on ibrutinib monotherapy for first line treatment of chronic lymphocytic leukemia (CLL).

Case presentation

A 73-year old male with a history of CLL (diagnosed in March 2018) presented to the emer-

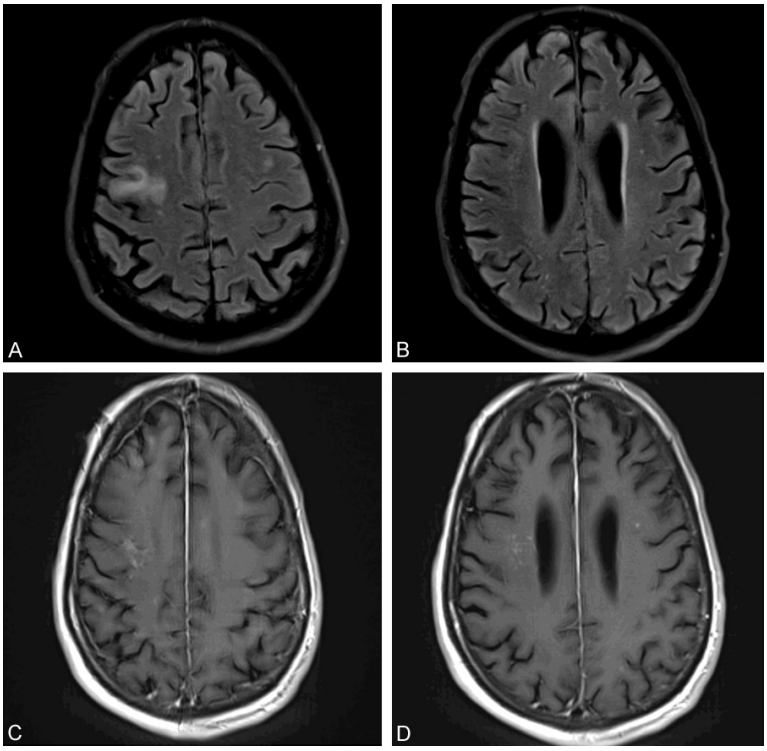

Figure 1. Brain MRI of the patient following ibrutinib therapy for 6 weeks. A. A FLAIR image showing a white matter hyperintensity lesion in the posterior right frontal lobe with the involvement of the subcortical U-fibers. B. A FLAIR image displaying multiple bilateral and asymmetric hyperintense white matter foci. C. A T1 post contrast image showing heterogenous enhancement of the right frontal lobe white matter lesion. D. A T1 post contrast image demonstrating the scattered bilateral and asymmetric foci of white matter enhancement, some corresponding to the foci of white matter signal abnormality on FLAIR images.

gency department in September 2018 with complaints of altered mental status, decreasing independence in activities of daily living, a fall, and confusion. These symptoms began two weeks after starting ibrutinib therapy for the treatment of CLL. The patient was started on ibrutinib 420 mg daily as the first line, single-agent therapy for RAI stage III CLL in August 2018, six weeks before his presentation with the progressive neurologic symptoms. The physical examination showed normal vital signs and no acute distress. The neurological examination was notable for left upper extremity weakness (4/5). He was alert and awake but was disoriented to time. He also had a decreased attention span, could not spell "world" backwards, and had both impaired immediate and delayed recall. The laboratory results indicated normal electrolytes, bilirubin, and liver enzymes. The erythrocyte sedimentation rate was 92 mm/hr, the creatinine levels were 1.5 mg/dL, the blood glucose levels were 152 mg/dL, the white blood cells counts were 9,000 cells/mm^3 with an absolute lymphocyte count 6000 cells/mm^3, the hemoglobin levels were 11.7 g/dL, and he had normal platelets, prothrombin time, partial thromboplastin time, and urinalysis. The generalized lymphadenopathy and splenomegaly seen prior to the initiation of ibrutinib had now resolved. The ibrutinib was discontinued and supportive care provided.

The magnetic resonance imaging (MRI) of the brain revealed findings concerning for PML (**Figure 1A-D**). A lumbar puncture was obtained, and the cerebrospinal fluid (CSF) showed a normal cell count, normal glucose levels, and slightly elevated protein. The CSF and blood tests were negative for human immunodeficiency virus (HIV), herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV) and enterovirus. The cytology and immunophenotyping of the CSF by flow cytometry were both negative for malignancy or CLL. The JC virus testing by polymerase chain reaction (PCR) on the first CSF specimen came back as inconclusive. A repeat spinal fluid PCR for JC virus done a week later came back negative. A third CSF analysis was also negative for JC virus. Hence, it was decided to do a brain biopsy of the right frontal lesion. The brain biopsy confirmed the diagnosis of PML (**Figure 2A-C**). The patient was referred out to receive adoptive T cell therapy for PML in a clinical trial, but he died from progressive disease several weeks later.

Discussion

What is known about the association of ibrutinib and PML in patients with CLL?

A literature review confirms that PML is an extremely rare event in patients receiving ibrutinib therapy for CLL. There are only a few cases

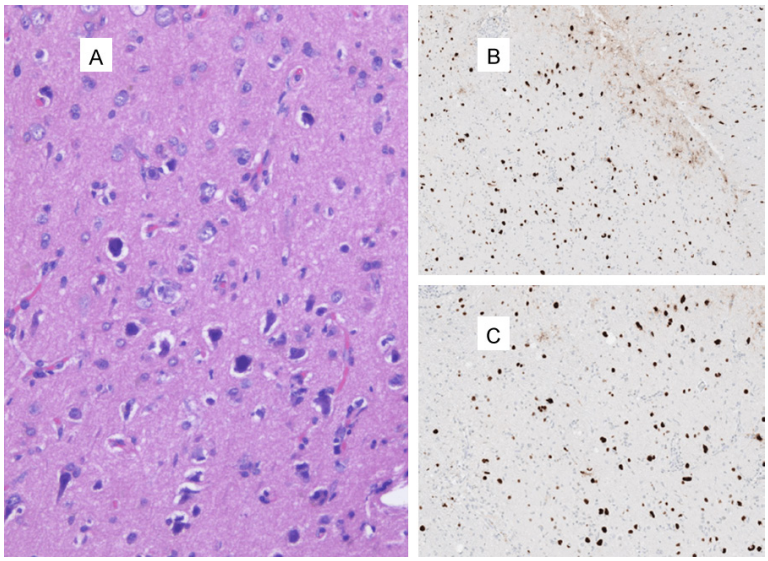

Figure 2. Brain biopsy, H & E stain 20×: cortex with increased microglia and gliosis with a subset of cells showing nuclei with basophilic glassy chromatin also known as viral cytopathic effect (A). Brain biopsy, SV40 immunostain, 10× (B) and 20× (C) - the cortex shows cellular nuclei with the viral cytopathic effect, positive for SV40 (a surrogate marker for the JC virus).

which can cause an extended period of immunodeficiency that can subsequently increase the risk of rare and unusual infections, including PML. The clinical use of ibrutinib continues to expand to other B cell indolent lymphomas, including lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia), marginal zone lymphoma, and mantle cell lymphoma. With its increased utilization, time will tell if the widespread use of ibrutinib is associated with an increased frequency of PML cases in patients with indolent lymphomas.

What do clinicians need to know about the diagnosis of PML in general?

reported, as of the time of our writing. In a case report by Lutz, et al., a patient with CLL was being treated with rituximab (along with several other agents), with the last course of rituximab documented three years prior. When the patient was switched to ibrutinib, the patient subsequently developed PML [7]. A second case was published by Hsiehchen, et al. in which the patient developed PML after being on prolonged ibrutinib therapy, with a low burden of CLL disease [8]. In a series of five cases of PML among ibrutinib treated patients published by Bennett et al., four patients (80%) had previously received a rituximab-containing regimen and one had received chlorambucil before ibrutinib was initiated [9]. To the knowledge of these authors, this is the first case of PML to be reported with a symptom onset after a few weeks of first line ibrutinib single-agent therapy for CLL.

The indications of ibrutinib as a therapy for CLL have been drastically increased. While it was initially approved as the first-line agent *only* for high risk CLL with 17p deletion [10], it has since received approval as the first-line therapy for all patients with CLL [11]. In CLL, therapy with ibrutinib is continued until the disease progresses or unacceptable toxicity occurs. This makes it a long-term therapy,

In addition to the clinical features described in our case, neuroimaging findings in PML can be characteristic of the disease. An MRI is the most sensitive tool to screen suspected PML patients [12]. The PML lesions are usually multifocal and asymmetric in the periventricular and subcortical white matter but may involve the corpus callosum, brainstem pyramidal tracts, and cerebellum. Involvement of the subcortical U fibers is frequently seen [13-15]. The lesions classically do not enhance with contrast and do not display mass effect or hemorrhage. However, contrast enhancement has been reported with natalizumab-associated PML, immune reconstitution inflammatory syndrome after retroviral therapy for AIDS, and has been linked with improved survival [13, 14]. When PML is suspected, the workup should include a spinal fluid analysis to rule out other infectious or inflammatory etiologies, and JC virus testing should be performed using PCR. In the case of the JC virus, PCR testing is usually highly specific (92-100%), but the sensitivity of this modality is markedly lower (72-92%), and a negative test should not exclude PML infection [16]. It is not uncommon to find negative CSF and JC virus PCR results in patients with AIDS who are on antiretroviral therapy [16]. Therefore, it is recommended to

repeat JC virus PCR testing in the CSF, even if the results of the initial testing were negative. A brain biopsy is the next step following repeated negative JC virus PCR in the CSF. A brain biopsy is the most specific test and has 100% specificity for PML.

How good is CSF testing of the JC virus using PCR in patients with hematologic malignancies?

In a report of sixteen patients with hematologic malignancy-associated PML, four patients (25%) exhibited false negative CSF test results and required brain biopsies to establish the diagnosis [17]. This report, and our case, illustrate the fact that CSF testing can be falsely negative in PML patients with hematologic malignancies, and will thus require a brain biopsy in a sizable fraction of patients to get to the diagnosis. If clinical suspicion persists, despite multiple negative CSF results, a brain biopsy is therefore indicated.

What is the treatment and prognosis of PML patients with hematologic malignancies?

PML is a rare complication in the treatment of hematologic malignancies, with most of the cases occurring after hematopoietic stem cell transplants (HSCT) or after the use of monoclonal antibodies for the treatment of indolent lymphomas [18]. Cases involving the development of PML associated with HSCT have been found to have better outcomes compared to non-HSCT cases, most likely as a result of immune reconstitution following HSCT [18]. There is no specific or curative treatment for PML. The condition is almost invariably fatal with a median survival of two months following the diagnosis [17, 18]. The aim of the therapy is to reconstitute the immune system, which involves stopping all immunosuppressive therapy. It is nearly impossible to quickly recover immunity against the JC virus, due to a deeply paralyzed cell-mediated immune system in this setting as a result of the cancer treatment. BK virus specific adoptive T cell therapy [19] and donor lymphocyte infusion have been tried without definitive success. Novel effective therapies are urgently needed for this dreadful disease.

Conclusion

The ibrutinib use in our patient with CLL was associated with a fatal case of PML. The mechanism behind the underlying viral reactivation after ibrutinib use in CLL is unknown. The cause-effect relationship with ibrutinib and PML is hard to establish because PML is also known to occur in indolent hematologic malignancies even without treatment [17, 18]. Nevertheless, clinicians need to be aware that new onset neurologic symptoms in patients with CLL receiving ibrutinib could be due to PML. The diagnosis of PML in this setting is challenging and may require a brain biopsy if clinical suspicion remains high despite negative PCR results for the JC virus in the CSF. The prognosis remains dismal with or without therapy.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chakra P Chaulagain, Department of Hematology-Oncology, Myeloma and Amyloidosis Program, Maroone Cancer Center, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd, Weston 33331, Florida, USA. Tel: 954-659-5840; Fax: 954-659-5810; E-mail: CHAULAC@ccf.org

References

[1] Tan CS and Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 2010; 9: 425-37.

[2] García-Suárez J, de Miguel D, Krsnik I, Bañas H, Arribas I and Burgaleta C. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. Am J Hematol 2005; 80: 271-81.

[3] Goldberg SL, Pecora AL, Alter RS, Kroll MS, Rowley SD, Waintraub SE, Imrit K and Preti RA. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 2002; 99: 1486-8.

[4] Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, Laubach J, Bawn SD, Gordon LI, Winter JN, Furman RR, Vose JM, Zelenetz AD, Mamtani R, Raisch DW, Dorshimer GW, Rosen ST, Muro K, Gottardi-Littell NR,

Talley RL, Sartor O, Green D, Major EO and Bennett CL. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the research on adverse drug events and reports project. Blood 2009; 113: 4834-40.

[5] Gonzalez H, Bolgert F, Camporo P and Leblond V. Progressive multifocal leukoencephalitis (PML) in three patients treated with standard-dose fludarabine (FAMP). Hematol Cell Ther 1999; 41: 183-6.

[6] Novero A, Ravella PM, Chen Y, Dous G and Liu D. Ibrutinib for B cell malignancies. Exp Hematol Oncol 2014; 3: 4.

[7] Lutz M, Schulze AB, Rebber E, Wiebe S, Zoubi T, Grauer OM, Keßler T, Kerkhoff A, Lenz G and Berdel WE. Progressive multifocal leukoencephalopathy after ibrutinib therapy for chronic lymphocytic leukemia. Cancer Res Treat 2017; 49: 548-552.

[8] Hsiehchen D, Arasaratnam R, Raj K, Froehlich T and Anderson L. Ibrutinib use complicated by progressive multifocal leukoencephalopathy. Oncology 2018; 95: 319-322.

[9] Bennett CL, Berger JR, Sartor O, Carson KR, Hrushesky WJ, Georgantopoulos P, Raisch DW, Norris LB and Armitage JO. Progressive multifocal leucoencephalopathy among ibrutinib-treated persons with chronic lymphocytic leukaemia. Br J Haematol 2018; 180: 301-304.

[10] Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Devereux S, Barr PM, Furman RR, Kipps TJ, Cymbalista F, Pocock C, Thornton P, Caligaris-Cappio F, Robak T, Delgado J, Schuster SJ, Montillo M, Schuh A, de Vos S, Gill D, Bloor A, Dearden C, Moreno C, Jones JJ, Chu AD, Fardis M, McGreivy J, Clow F, James DF and Hillmen P. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014; 371: 213-23.

[11] Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, Simkovic M, Samoilova O, Novak J, Ben-Yehuda D, Strugov V, Gill D, Gribben JG, Hsu E, Lih CJ, Zhou C, Clow F, James DF, Styles L and Flinn IW. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019; 20: 43-56.

[12] Küker W, Mader I, Nägele T, Uhl M, Adolph C, Klose U and Herrlinger U. Progressive multifocal leukoencephalopathy: value of diffusion-weighted and contrast-enhanced magnetic resonance imaging for diagnosis and treatment control. Eur J Neurol 2006; 13: 819-26.

[13] Smith AB, Smirniotopoulos JG and Rushing EJ. From the archives of the AFIP: central nervous system infections associated with human immunodeficiency virus infection-radiologic-pathologic correlation. Radio Graphics 2008; 2: 2033-2058.

[14] Whiteman ML, Post MJ, Berger JR, Tate LG, Bell MD and Limonte LP. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation. Radiology 1993; 187: 233-240.

[15] Collazos J, Mayo J, Martínez E and Blanco MS. Contrast-enhancing progressive multifocal leukoencephalopathy as an immune reconstitution event in AIDS patients. AIDS 1999; 13: 1426-8.

[16] Marzocchetti A, Di Giambenedetto S, Cingolani A, Ammassari A, Cauda R and De Luca A. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. J Clin Microbiol 2005; 43: 4175-7.

[17] Neil EC and DeAngelis LM. Progressive multifocal leukoencephalopathy and hematologic malignancies: a single cancer center retrospective review. Blood Adv 2017; 1: 2041-2045.

[18] Herrera AD, Ayyappan S, Jasra S, Kornblum N, Derman O, Shastri A, Mantzaris I, Verma A, Braunschweig I and Janakiram M. Characteristics and outcomes of progressive multifocal leukoencephalopathy in hematologic malignancies and stem cell transplant - a case series. Leuk Lymphoma 2019; 60: 395-401.

[19] Muftuoglu M, Olson A, Marin D, Ahmed S, Mulanovich V, Tummala S, Chi TL, Ferrajoli A, Kaur I, Li L, Champlin R, Shpall EJ and Rezvani K. Allogeneic BK virus-specific T cells for progressive multifocal leukoencephalopathy. N Engl J Med 2018; 379: 1443-1451.